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CANCER—A BIOLOGICAL APPROACH*

III. VIRUSES ASSOCIATED WITH NEOPLASTIC CONDITIONS

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There is still an active body of opinion that would regard cancer as a parasitic disease due to infection of cells by extrinsic viruses. Such an attitude has the great attraction that it suggests straightforward approaches to the prevention of cancer by immunological methods and holds out more hope of an eventual effective chemotherapy. As various writers have pointed out, the claim that some neoplastic processes are due to virus infection is not inconsistent with a recognition of the overriding importance of somatic mutation. Any claim that all cancers are of infective character is unjustified and frankly absurd in the present state of knowledge.

It has never been easy to define a virus, and the recognition of provirus in bacteria, with the convincing evidence that it is intimately built into the host's genetic mechanism, has now made it even more difficult. Any definition must cover the fact that there are two very different systems from each of which by appropriate manipulations a continuing sequence of typical virus infections may be produced. These are respectively the infective particle and the infected host cell.

A virus, in the conventionally understood form of a population of infective virus particles, can be defined as a self-replicating agent or organism smaller than bacteria and capable of multiplication only within living susceptible host cells. It may be desirable to add certain qualifications when we have to discuss demonstrable or hypothetical self-replicating subcellular entities. A virus particle must be shown to carry specific patterns in protein and nucleic acid which are different from those of the host cell and which are not derived genetically from the host species or any species related to it.

At a certain stage of infection, host cells may contain no virus demonstrable by the classic method of breaking up the cell and inoculating the product into other susceptible cells. There is other evidence that at this stage the cells do not contain formed virus particles. Under certain circumstances this phase may be prolonged. Its existence can be recognized either by providing a situation where infective virus particles will develop and be identified by standard methods or by demonstrating specific virus antigen in or liberated from the cells.

In general a virus (in the sense covering both the infective and vegetative phases) can be recognized only if it produces cytopathogenic effects in some type of host. It is by no means necessary, however, that intracellular production of virus or virus constituents should always be associated with observable cellular changes.

Much of the discussion of a virus theory of cancer has been based on these difficulties of definition. The essential problem, however, is to decide whether the virus theory of cancer provides ideas which will allow (*a*) more effective generalization as an aid to the understanding of cancer, or (*b*) effective approaches to prevention or cure that would not be available if other views were held.

The incentive to consider whether all malignant neoplasms are the result of virus infection is derived from the fact that active proliferative lesions may be experimentally produced in birds and mammals by infection with a few typical viruses. The epidemiology of these conditions in nature is consistent with transfer of virus from one host to another by one of the classical methods. There are many other types of neoplasm in which there is no such association with overt virus infection. It is the contention of those supporting the virus theory that in this latter group virus is present, but, because it is normally in the vegetative phase or for other technical reasons, it cannot be observed by conventional techniques.

In this discussion we may deal with the relevant data under four headings: (1) The character of proliferative lesions produced by unequivocal viruses such as fibroma and fowlpox viruses. (2) The significance of the complex of conditions in fowls which includes lymphomatosis and filterable sarcomata. (3) The development of malignant lesions from virus-produced papillomata. (4) The changed susceptibility of proliferating or neoplastic tissue to virus multiplication and damage.

Proliferative Lesions Produced by Virus Infection

It is a commonplace that the gross effect of virus infection in vertebrate tissues is to produce varying degrees and mixtures of cellular proliferation and cellular necrosis. This can be seen in almost diagrammatic form in the lesions produced by different viruses on the chorioallantois. Typical strains of fowlpox give grossly proliferative lesions without necrosis. A neurotropic strain of vaccinia will give a pock with only a thin margin of hyperplastic and proliferating cells and a broad central crater of necrotic material (Beveridge and Burnet, 1946).

Fibroma virus in rabbits may be taken as typical of viruses with predominantly proliferative lesions. Morphologically it is a large pox-type virus; it is presumably spread by biting insects, and is in every sense a thoroughly "typical" virus. The characteristic lesion is composed of healthy-looking fibroblast-like cells and contains much infective virus. Antibody production can be demonstrated,

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and presumably as a result of an immune response the fibromatous lesions regress within a month or two and leave a solid immunity to reinfection. There is no evidence that malignant change ever occurs in the lesions.

This condition poses the general question of how or why a virus induces a cell type to proliferate, in this case almost like a neoplasm. Answers can fall into two categories. The first is to be satisfied with obtaining an accurate range of experimental data on the extent of proliferation produced on different types of tissue by the viruses selected for study and to look for any correlations with other observable qualities of the viruses and cells concerned. The second is to regard the proliferative lesion as a deviation from the normal control of form exercised by the organism as a whole and to use the phenomena in an attempt to understand both the nature of virus action on the cell and the process by which control of the cells' growth is lost during the active phase of the lesion.

In the present discussion we are concerned especially to see in what ways the simple proliferative lesion produced by fibroma virus can provide helpful analogies to what occurs in tumour production. In the fibroma lesion there is no evidence for or against the occurrence of a somatic mutation allowing release of a specific control. We must assume the release of a control, and the simplest hypothesis is that the virus after entering the cell uses, binds, or inactivates a component of the cell which plays an essential part in the process of control. Of the available suggestions the most attractive is to use Weiss's concepts of cellular interactions and to suggest that this type of virus infection results in the cell losing its normal function of maintaining or liberating the markers which convey information of its presence to adjacent cells. These would leave the infected cell representing a (non-existent) gap, which adjacent cells would replicate to fill and in their turn be infected. On this view one could have a mass of cells all "unaware" of the existence of any contiguous cell and therefore proliferating at the maximal rate allowed by nutritional and other still existent controls. An essential feature of this hypothesis is that the same result would appear if the control affected by virus infection were abrogated as a result of a corresponding somatic mutation.

The Shope Papilloma and its Malignant Changes

The naturally occurring virus papillomata of cotton-tail rabbits seem to result from simple transfer of virus from an affected animal to a mildly traumatized area on a susceptible one. The lesions contain infective virus and large amounts of a DNA nucleoprotein, which appears to represent the effective virus. The number of such nucleoprotein particles is, however, enormously larger than the number of minimal infective doses. The lesions are papillomata resulting from proliferation of skin epithelium with various secondary changes. Specific antigen is produced with demonstrable antibody response, and some of the growths retrogress slowly.

The main interest of this virus in relation to neoplasia depends on two findings: (1) Infection of domestic rabbits gives rise to large papillomatous lesions in which little or no virus can be demonstrated. It has been held that this provides a prototype of the condition present in those cancers where no virus can be isolated. (2) The lesions produced either in cotton-tails or domestic rabbits frequently become carcinomatous, especially if the skin involved has been treated with a chemical carcinogen as well (Rous and Kidd, 1938).

The non-infective character of the lesions in the domestic rabbit would be best interpreted as a stabilized vegetative phase in which specifically patterned virus components are being produced but for one reason or another are not being fabricated into complete infective virus. From analogy with the findings in regard to non-infectious haemagglutinin in influenza virus infections it may be that the essential defect is an unbalanced production of virus protein without equivalent replication of the DNA component. The point of special importance is that the proliferative character of the lesion, which is as marked in domestic rabbits as in cotton-tails, must depend on the earlier stages of the process of virus replication, since the fabrication and liberation of complete virus particles does not occur. With the proliferation of infected but otherwise undamaged cells, virus patterns in DNA and protein will be distributed to descendant cells and will be enabled to exert in them whatever deviation of control is needed to maintain the proliferative process.

In cotton-tail rabbits many of the growths fail to retrogress, and about 25% become frankly malignant. With the change to carcinoma, virus can no longer be found in the growths (Syverton *et al.*, 1950). Extensive studies have been made in domestic rabbits of the capacity of the virus to provoke carcinomata in skin areas converted to a precancerous state by treatment with tar. From the history of a transplantable carcinoma V2 produced in this way, it appears that, though no free virus was present, all rabbits bearing the tumour for its first 22 passages developed antibody against papilloma virus. After 46 passages, however, the capacity to produce antibody had disappeared. This tumour was dependent on the existence of vegetative virus, but when the appropriate somatic mutation arose the continuation of virus action became both unnecessary and impossible.

Avian Lymphomatosis and Related Conditions

In domestic fowls, and perhaps in other birds, there is a wide range of neoplastic processes involving mesenchymal cells from which with varying degrees of difficulty noncellular infectious material can be obtained. The epidemiology of the group is still rather obscure, but everything points to the conclusion that viruses of this complex do spread by one process or another from bird to bird. The viruses concerned are highly labile genetically, and it is perhaps best to regard the most extensively studied types, the Rous sarcoma and Beard's erythromyeloblastosis, as laboratory variants rather remote from natural strains.

It has been known for many years that Rous tumours vary greatly in their filterability. Duran-Reynals (1953) considers that this is largely related to the age of the host. In very young birds haemorrhagic necrotic lesions with much filterable virus is the rule. In old birds slower-growing tumours containing no extractable virus are commonly found. These are just as effective stimulants to antibody formation as are tumours that provide free virus.

Probably the most rewarding way to look at the lymphomatosis viruses of birds is to recognize the different requirements for cell-to-cell transfer if a proliferative process is involved. The standard teaching on the natural history of viruses is that we have a regular alternation of phases. The infective particle, the conventional "virus," is a unit specifically evolved to transfer infection to a new host cell. It is immaterial whether this is another cell of the same host organism or a cell of another individual in which infection is being initiated. Within the susceptible cell we have the vegetative phase, in which replication of all the specifically patterned components needed for infective virus is going on. It has been one of the important recent findings of virology that it is by no means inevitable that initiation of cellular infection must be followed by the production and liberation of a new brood of infectious virus. With highly virulent types, and especially those adapted to specially susceptible laboratory hosts, this condition may be approached.

In nature probably a very large proportion of cells into which virus enters support only a limited phase of the process of replication and produce no infective virus. Under most circumstances this will entail the elimination of the virus concerned, but conditions may be different if the incompletely infected cell proliferates as a result of some change induced by the infection. The vegetative virus can then progressively infect more and more cells, either descendants or conceivably by some form of cytoplasmic fusion with cells of other lines. If at the end of such an internal spread opportunity arises for the production of a proportion of infective particles that can reach new individual hosts, there is a clear possibility that the mechanism may have survival value for the virus. As in so many other areas of biology, we find what looks like a degeneration put to biological service and providing a new niche for survival.

The status of the Bittner milk agent in relation to mammary cancer in mice is not yet clear. If it is introduced very early in life it gives rise to mammary cancer at a late stage in mice whose inheritance and endocrine experience are appropriate. There are suggestions that it may arise spontaneously, and there is no doubt that mammary carcinoma can arise in its absence. It is an interesting point, possibly due to an inability of the virus to become implanted unless it enters the body at a stage when immunological tolerance can develop, that no antibodies against the virus have been detected in mice. The general picture one receives is of a virus of very low grade that has found a way of persisting in mouse tissues analogous to that of lymphocytic choriomeningitis virus. As such it has an opportunity to act as an effective link in a chain of abrogated controls leading to the development of mammary cancer.

The other alternative, which is equally applicable to the virus that can transmit leukaemia to mice inoculated on the first day of life (Gross, 1954), is that these mouse agents are not descendants of autonomous viruses, but represent pathologically active subcellular organelles whose pattern has been derived relatively recently from a mouse genetic mechanism. This has been a common speculation for many years, but no one has been able to provide definitive criteria which will establish such an origin.

A point relevant to the lymphoma–leukaemia group of conditions in domestic fowls and laboratory mice is the possibility that there seem to be rather numerous strains in both species in which the overall genetic control of lymphoid cell proliferation is abnormally weak.

Changed Susceptibility of Proliferating Cells to Virus Attack

In recent years the oncolytic action of certain viruses has raised hopes that eventually we may see therapeutic use of viruses which, while lethal for tumour cells, have no action on normal tissues. There are other changes in cell circumstances that may lead to increased susceptibility to virus action, and it is perhaps significant that two of them are associated with diminished control of growth. Virus fibroma lesions in rabbits are infected and rapidly destroyed by some of the encephalitic viruses, including Semlikii Forest and MVE, which have no more than trivial action on rabbit tissues generally (Ginder and Friedewald, 1951). Monkey kidney cells *in vivo* do not support multiplication of poliovirus and suffer no damaging effect (Kaplan, 1955). When prepared for tissue culture they represent the medium of choice for growth and recognition of the virus. The HeLa strain of human cancer cells is susceptible to a wide range of viruses, and it is usual to find that transplantable mouse tumours are more susceptible to many viruses than normal mouse tissues.

Koprowski (1955) has introduced an important new point in showing that when an ascites tumour broadens its range of hosts—that is, loses an antigenic individuality marker—it concomitantly develops an increased susceptibility to the cytopathogenic action of several viruses. It may be significant, too, that rapidly growing embryonic tissues where control obviously takes a different form to that of the adult are highly sensitive to virus action. And one may wonder whether in the central nervous system, with its undue susceptibility to many viruses, there may be another clue to this general problem.

When increased susceptibility to viruses becomes evident it is to their necrotic action, not to their effect in increasing proliferation. If simple proliferation is, as we have suggested, due to the relaxation of what might be called proximity control, then it appears that when this control is lost there is no other point at which a number of viruses (of the arthropod-borne group) can be checked once they enter the cell. For reasons that we have discussed in relation to the typical "tumour viruses" the block which tends to be associated with proliferative rather than necrotizing action must lie at a stage just before the completion of virus replication. It is of considerable interest that at the present time there is a strong tendency for virologists to regard the final fabrication of virus as a function of the cell surface. This is particularly well established for influenza virus. In the allantoic cavity the whole process takes place on the free surface of the cell. This is the only surface where there is not a constant proximity to the living surface of other cells. It is too early to make any hints on how a proximity control might also function as a barrier preventing the completion of virus particle production, but it is hard to believe that it will not eventually be found to do so.

Development of Malignant Characters by Cells in Tissue Culture

One of the most decisive arguments against a necessary part being played by viruses in carcinogenesis is derived from the findings that pure cell lines maintained in tissue culture can become malignant. Many examples of this have recently been reported in strains of fibroblasts from mice or rats, but perhaps the most interesting report is that of Earle's group (Sanford *et al.*, 1954). They established a line of fibroblasts from a single cell and from this line developed eight clones which were studied for their capacity to produce sarcomata when inoculated at various stages of culture into mice of the homologous strain. After several passages six of the eight clones had given typical tumours. The most consistently active of these, Line VII, and a strain which had produced no tumours, Line III, were then selected for detailed study. Line VII produced sarcoma in 97% of the mice inoculated, Line III in only 2 out of 146 inoculated. If *x*-irradiated mice were used, however, over 40% of tumours were obtained from Line III, and these tumours could subsequently be passed in normal mice. The two lines, VII and III, in addition to this difference in transplantability also showed clear differences in cellular morphology. The phenomena are what would be expected on the hypothesis of somatic mutation, but would require a fantastic series of secondary *ad hoc* assumptions to be interpreted as manifestations of virus infection.

Although the evidence can naturally never be complete there is very much to suggest that all, or almost all, of the cell lines derived by virologists from normal human tissues become malignant as they develop facility to grow indefinitely in tissue culture. It is characteristic that at this stage they become susceptible to practically the same range of viruses as HeLa cells and lack any special susceptibility for viruses which naturally infect their cells or origin.

Summary

The general picture emerging from this discussion of the "cancer viruses" is that these represent simply one rather potent means by which what is functionally equivalent to a somatic mutation can be produced. In the well-studied rabbit papilloma there is good evidence that when malignancy is fully established virus cannot grow in the tumour cells. The analogy with azo-dyes and the development of hepatoma is extraordinarily close.

Where a virus produces a proliferative lesion a unique opportunity exists for the development of a situation which probably arises commonly enough in other types of virus infection but cannot be demonstrated. This is the persistence of a "vegetative state" in which production of virus antigen goes on, presumably with replication of the associated nucleic acid more or less in tempo with cellular multiplication, but no production of infective virus. Since in these proliferative lesions infected cells are the progeny of infected cells there is no necessity for the production of infective particles to transfer infection from one cell to another. In all probability any low-grade virus which can

find a cell, either normal or one or more stages on the way to loss of control, in which it can produce proliferative effects will have some or all of the qualities of a cancer virus. Probably all viruses have some capacity to provoke proliferation—the uniform structure of the chorioallantoic lesions speaks for this—but the converse claim that all proliferative processes are due to viruses is quite untenable.

IV. PRACTICAL APPLICATIONS

The only social justification of generalization in science is to provide firmer basis for human action. If the picture of somatic mutation as the basis of malignant disease is correct what are the implications at the practical level? More specifically, does it provide leads regarding research which might eventually allow the development of new techniques for the prevention, diagnosis, or cure of cancer?

Prevention

One of the most heartening developments in medicine has been the recognition that a very large proportion of lung cancer has a definable aetiology and, in principle at least, is preventable. This underlines the potential importance of continued search for aetiological agents of environmental origin. If a somatic mutation cannot be reversed it is of the utmost importance that the conditions under which it is either provoked or given the conditions to allow it to prosper unduly should be understood and counteracted.

Despite continuing assertions that there is as yet no absolute proof of the significance of cigarette smoking, the available evidence suggests that the position in regard to lung cancer is, in fact, relatively clear.

There are two types—one described as adenocarcinoma, which occurs with equal frequency in males and females and for which there is no evidence of environmental influence; the second, comprising squamous-celled and anaplastic carcinomas, is that which is responsible for the recent great increase in lung cancer. This increase is real and is directly related to two environmental factors, cigarette smoking and the degree of urbanization of the environment. A good case can be made for Stocks and Campbell's thesis (1955) that the effective cause of lung cancer is the amount of common carcinogen, 3:4-benzpyrene, in the air inhaled, including of course air inhaled while smoking. In non-smokers there are nine cases of urban lung cancer to one in the country. The ratio diminishes as smoking increases until for heavy cigarette smokers the same high incidence is found in the country as in the town. The preventive approach is therefore quite clear-cut and probably socially impossible to implement. Cigarette smoking needs to be rendered unpopular by every acceptable means, and the greatest attention must be paid to reducing the products of incomplete combustion of fuel that are liberated into the air. It is a good rule that smoke, whether from a factory chimney, a diesel exhaust, or a cigarette, is dangerous and undesirable.

There are a number of other indications of environmental factors being important in the production of cancer, and there may well be some more unpleasant surprises in store for us. There is, for instance, much interest in but no solution of the fact that Indonesians have far less gastric cancer than Europeans or Chinese and much more liver cancer. The suggestion that dietary factors are involved is insistent, but no one has provided a likely answer in any detail.

More immediately important is the part played by ionizing radiation, whether from x rays, from atomic explosions, or from the entry of radioactive material into the body. When dealing with fair-skinned people, one could add the ultraviolet component of sunlight as a penetrating radiation so far as the superficial cells of the body are concerned. The high incidence of relatively mild and tractable skin cancer in regions like Queensland, where there is plenty of sunshine, has been well known for years.

One of the important aspects of the somatic mutation theory of cancer is the way it brings into the same focus the two important harmful effects of ionizing radiation, carcinogenesis, and genetic damage. Whether acting on the nuclei of germ cells or on the nuclei of the somatic cells of the body, the effect of radiation is the same—random damage to a relatively large assemblage of complex genetic mechanism. It is as if a bullet were fired at random into an automatic telephone exchange. The results would have only a very small relationship to the size or speed of the bullet, but, depending on wholly accidental factors as to where the hit occurred, they might range from no functional effect at all through various types of minor or major malfunction to complete breakdown. As we have discussed, the only type of somatic mutation in man that can be observed is one leading in the direction of cancer. Many other types undoubtedly occur, but there can be no overt evidence of their presence. Germ-cell damage also has only a limited number of ways in which it can be recognized; like damage to somatic cells, it is in general only recognizable when it is of minor degree allowing the production of offspring in whom a specific defect can be recognized. Just as genetic damage may only become manifest in distant generations so somatic damage may have no immediate effect but may lead to the accumulation of a stock of mutant cells all one or more steps nearer to malignant change.

There is no doubt that every type of ionizing radiation has a measurable mutagenic power and that the effect is cumulative—that is, it is just as dangerous to receive 365 units of radiation in 1-unit doses daily over a year as to receive the full dose in a minute. It is impossible, therefore, to say that any dose of radiation is harmless. On the other hand, very high doses are needed to produce malignant change in a large proportion of animals experimentally exposed. Radiologists in the early days were occupationally liable to skin cancer. Now with better protection but much more powerful machines they are still subject to an undue mortality from leukaemia (March, 1950). Large therapeutic doses of x rays, notably for ankylosing spondylitis (M.R.C., 1956), have been shown to be responsible for the development of leukaemia in a significant proportion of cases.

Increasing Exposure to Ionizing Radiation

The only fully established chronic effect of the atom-bomb explosions over Japan was the development of leukaemia in a proportion of the survivors some years later. At the present time leukaemia is the only form of malignant disease other than cancer of the lung that is showing a steady increase. Much thought is being given to the possibility that some, or all, of this increase can be ascribed to increasing exposure to ionizing radiation. There have been two disquieting recent reports. First, that children of mothers who were exposed to diagnostic x rays of the pelvic region during the relevant pregnancy show a much higher incidence of leukaemia and other forms of malignant disease than a control series (Stewart *et al.*, 1956); and, second, that in comparing the history of patients with myelogenous leukaemia with those suffering from chronic lymphatic leukaemia the former group showed a significantly greater amount of exposure to diagnostic x rays (Faber, 1956). These results make it urgent to extend such studies so as to obtain as soon as possible a sound assessment of the danger associated with diagnostic and therapeutic exposures to x rays. It may turn out to be trivial, but equally it may come to be regarded as of sufficient importance to demand revolutionary changes in radiological practice.

Other indications of the carcinogenic activity of ionizing radiation in man can be found in the recently described cases of carcinoma of the thyroid in children treated locally with x rays on the assumption that an enlarged thymus was responsible for symptoms (Clark, 1955). Equally relevant is the classical account (M.R.C., 1956) of the occurrence of bone sarcomata in technicians using radium paint in the manufacture of luminous watch-dials, etc. Extremely minute amounts of radium were involved. Since one of the important products of atomic fission, ^{90}Sr, is, like radium, selectively concentrated in the bones and has a half-life of 28 years, an increasing incidence of bone tumours may be one of the first indications of a dangerous increase in fission by-products.

A full-scale atomic war would have social consequences that would end scientific medicine for generations, and it would be useless to attempt any discussion of its medical sequelae. It is legitimate, however, to consider the implications of the inevitable great increase in the industrial use of nuclear power and the wide distribution of radioactive isotopes which is bound to accompany it. All recent reports stress the problems associated with the large amounts of radioactive waste products that have to be disposed of in the plants for chemical treatment of metal "fuel" that has been used in reactors. So far methods of dealing with such problems seem to have been adequate, and it may be possible to continue to enforce the necessary discipline and control in the future. There is a real risk, however, that as more and more reactors are brought into production all over the world familiarity will result in relaxation of precautions and minor and major accidents increase. Already in Australia we have heard of industrial capsules of cobalt-60 being left for uninstructed adults or children to handle, in one case with the subsequent development of severe lesions.

There is unanimity of authoritative opinion that the global concentration of fission products from test explosions of atomic weapons, plus the limited release of radioactive material from industrial reactors, is at the present time and in the foreseeable future far below the danger level for genetic damage. There is much less evidence about the possible effect of the ^{90}Sr, which is selectively concentrated in bone, or ^{131}I, which, although an isotope of short half-life, may be concentrated sufficiently in the thyroid to produce serious local effects. It would seem highly desirable that careful watch should be kept on the incidence of tumours of bone and of the thyroid during the next decade. These, plus leukaemia, would be the most likely conditions to indicate that the liberation of radioactive material was becoming positively dangerous to health.

From the more general point of view, the last approach to the (partial) prevention of cancer seems likely to be a concentration of research on the mechanism of chemical carcinogenic action. The production of a somatic mutation is in itself unimportant unless conditions are such as to allow an extensive replacement of normal cells by descendants of the mutant type. It may emerge that there are ways by which these conditions can be controlled even if mutation is inevitable. There is, for instance, much to suggest that any form of chronic irritation and inflammation which gives rise to an increased turnover of epithelial cells in one of the vulnerable regions will increase the likelihood of the appearance of malignant change. Appropriate treatment of such conditions may well have an important place in the prevention of cancer.

Diagnosis

The problem of early diagnosis is an extremely difficult one, and if the somatic mutation hypothesis is correct it may, in principle, be even insoluble. Modern studies on the survival time of patients treated in various ways suggest that for many types of cancer the end-result depends on the type of malignant cell and is virtually uninfluenced by the particular form of treatment adopted (Jones, 1956). The only justification for special measures of early diagnosis is a reasonable certainty that the prognosis will be improved by such diagnosis. In view of the universal practice of excising or destroying all small lesions known or suspected to be early cancer, it may be quite impossible ever to make such an assessment. The invariable finding that very early lesions give much better survival rates than more advanced ones is by no means an adequate basis for demonstrating the importance and effectiveness of early diagnosis. If every malignant growth represents the result of a final mutational change occurring in one of numerous cells which have reached by successive mutation the penultimate stage, then effective treatment may well demand the excision of all these immediately vulnerable cells as well. Where the process of carcinogenesis has been confined to a limited region—clay-pipe cancer of the lip might be taken as a typical example—this may be very readily accomplished. In other situations it may be quite impossible simply because of our inability to recognize cells in the vulnerable state.

One of the academic and perhaps practical problems of the future is to find means of recognizing the extent to which intermediate changes on the road to malignancy have occurred. From the nature of the problem the only hope of recognizing such changes is the histochemical one. Mutations can give rise to general effects only when the mutant type constitutes a significant proportion of the order of 10% or more of the cells of its type in the body. A means must be available by which a much smaller proportion of aberrant cells can be recognized, and histological methods of some sort are the only ones that are at present conceivable.

It is the great virtue of Green's immunological approach that it more than any other theory of cancer provides indications for the direct experimental study of its implications. If the process is to a large extent a loss of serological markers, these changes can in principle be recognized by the use of Coons's (1954) methods with fluorescent antibody as used, for instance, by Weiler (1956) in the study of rat hepatoma. In the field of human pathology, very much might be expected from the production of a series of fluorescent antisera rendered specific by appropriate absorption, against as many organ-specific human antigens as it is practicable to prepare.

Conventional methods of histological examination for the detection of pre-cancerous change will always have their value, but if direct serological indications can be obtained it is most important that they should be elaborated immediately. It is a possibility that such studies would allow concomitant changes to be recognized which would eventually allow the use of simpler histological methods for their detection. The application of fluorescent antibody studies to exfoliated cells might add a further diagnostic criterion to this method of clinical study.

Curative Treatment

If somatic mutation is the key to the understanding of cancer there are grave restrictions to the possibilities of prevention and cure. Nature has only one way of eliminating harmful mutants—by genetic death. Mutation being basically a random process, there is no conceivable way by which a cell can be induced to undergo a specific back-mutation to eliminate the change. Even if in a sense carcinogens act by enforcing a specific mutation by loss, there is still no conceivable way by which the loss of genetic material can be replaced in the cells concerned. Therapy along somatic-genetic lines is therefore unthinkable.

Any therapeutic approach must be indirect and based on some exploitation of a physiological difference between the cancer cell and normal body cells. The chemotherapeutic approach to date has been almost wholly along such lines and suffers from one overwhelming intrinsic disadvantage, which may be put in oversimplified form—namely, that all anti-cancer drugs are also carcinogens. As has been discussed in regard to Law's (1952) work, the situation is analogous to that found with antibiotics and staphylococci. Every effective antibiotic is capable of assisting the emergence of a bacterial pathogen resistant to its action. Once a malignant process is well established, the cell population has become genetically heterogenous, and though 99% of the cells may be susceptible to some antimetabolite and immediate benefit result, experience to date has confirmed the theoretical prediction that elimination of all cancer cells will be impossible and that sooner or later a new generation of cells resistant to the formerly effective agent will become clinically evident.

A slightly more hopeful approach, which, however, is so dependent on the body's own resources that it has never been seriously propounded, is the immunological one. It is generally regarded as axiomatic that, since a cancer cell is of the body's own pattern, no effective immunological action against it is possible. In view of recent work, it is, however, conceivable that in many instances there is sufficient antigenic difference to be effective. In terms of the immunological ideas discussed in Part I, cell components, normally non-antigenic, may become so either by modification of antigenic pattern through the action of chemical agents capable of being bound to the component, including perhaps viruses or their products, or by being brought into a new relationship to the scavenging cells of the body. Somatic mutation with malignant or pre-malignant changes might allow either of these conditions to arise. If in terms of Green's theory the loss of self-markers is an important step in the progressive abrogation of control, it may become important to know whether the loss of an antigenic pattern with this effect is or is not associated with the emergence of a new and therefore foreign antigenic pattern. Green's view would be that a carcinogen plus host protein produced a new antigen but that malignancy is associated with the shedding of the new antigen by somatic mutation. Loss of any antigenic pattern may, however, be associated with the emergence of another.

It is by no means inconceivable that small accumulations of tumour cells may develop and because of their possession of new antigenic potentialities provoke an effective immunological reaction, with regression of the tumour and no clinical hint of its existence. It has also been suggested that the result of surgery for cancer may to a large extent be determined by the degree of resistance, presumably immunological in nature, against the tumour cells. Black *et al.* (1954) found a sharp correlation between the degree of lymphocytic infiltration in the tumour removed at operation and the likelihood of "cure" following surgery.

What is to be sought is some means whereby the protective mechanism of the body has its reactivity against minor deviations from self-patterns made more sensitive—the converse of the effect of cortisone in damping down immunological reactivity. One would guess that the desired capacity is determinable only by genetic means, but this is not necessarily so, and from many points of view research along these lines might be particularly valuable for its practical potentialities.

The use of specific antigens for immunization against cancer can be ruled out from the most elementary consideration of the position.

The orthodox treatment of cancer has always been based on a more or less clearly visualized somatic mutation theory. The objective has been first to excise from the body all cells which have taken on the new genetic behaviour, and, if that is impossible, to use any agent known or presumed to have a differentially destructive effect on the malignant cells. When eradication of the malignant cells is impossible there still remain medical and surgical measures which by one or another form of symptomatic relief will do much to make the final stages of disease more tolerable.

Under the circumstances theoretical considerations can have no special significance at the therapeutic level. The most satisfactory application of the very simple principles outlined above will have to be worked out on an empirical basis for each particular type of tumour and every possible opportunity taken to assess the results of treatment objectively. The only satisfactory way is to follow the after-history of treated patients till their death.

To one not directly associated with the surgery of malignant disease it is extraordinarily difficult to gain a clear picture of how much effect modern surgical and irradiation therapy has had on the death rate from cancer. The overall mortality statistics show little or no effect, and some recent analyses (Jones, 1956) of adequately studied series of some of the commoner types of tumour have found it very difficult to show that therapeutic action has greatly modified survival time. On the other hand, there is no doubt that published results of treatment for early cancer of lip, skin, breast, and cervix uteri show quite gratifying five-year survival percentages.

Perhaps the most pertinent query that is raised by this theoretical discussion is in regard to the use of various forms of ionizing radiation in treatment. Is it or is it not established that radiation influences the survival rate beneficially ? There is no doubt that appropriate dosage will cause differential destruction of large numbers of malignant cells. On the other hand, there is also a markedly destructive effect on cells of the lymphocytic series that would mediate any immunological resistance, and there is the carcinogenic effect of irradiation on normal cells. Obviously the practical usefulness of radiation therapy can only be established empirically.

Conclusion

There is little ground for optimism about cancer. Everything suggests that, somatic cells being what they are, the impact of the environment must inexorably lead to an accumulation of mutant cells, some of which will have malignant descendants if life persists long enough. Both the genetic character of the cells exposed and the intensity and type of the mutagenic stimuli from the environment will play a part. At the present time two types of environmental stimuli—the carcinogenic hydrocarbons from incomplete combustion processes and ionizing radiation—are steadily increasing in importance. It may eventually be possible to recognize other specific agents as being responsible for certain types of cancer which have not shown any special change of incidence in recent years. From the very nature of the processes concerned it is difficult to envisage effective means of utilizing such knowledge for the prevention of cancer. We are not likely to ban cigarette smoking and the use of diesel engines on the roads, or to stay the development of nuclear energy, just because these aspects of our mode of living indubitably increase the incidence of cancer.

We must work toward prevention and be prepared not only for failure but for a sharp increase in the incidence of cancer with the further elaboration of modern technology. If so, the medical problem of the future will be very largely to clarify the immense complexities that arise when we try to adopt the orthodox maxim, "Recognize the cancerous lesion as early as possible and excise it."

If what can legitimately be called pre-cancerous lesions are an inevitable development with increasing age it will need the greatest skill and judgment to devise and implement a policy which will provide the "greatest good to the greatest number." On the one hand, there are sound psychological, social, and economic reasons against the use of cancer-detection clinics to carry out relevant periodical examinations of all persons over the age of 40. There is, too, the underlying uncertainty regarding what is the real prognostic significance of borderline lesions—for example, intra-epithelial carcinoma in biopsies of the cervix uteri—and even greater doubts about the ability of any treatment to deal effectively with cancers whose histological character is undubitably malignant. All these points have to be weighed against the desire of all concerned to find and treat malignant growth at the stage at which it can be eradicated.

It would probably be wise to conclude that the diagnosis and treatment of cancer is one of those social problems that must be allowed to develop their own current solution under the various pressures of advancing knowledge, of changing public opinion, and of the enthusiasm and influence of advocates of this or that approach. A final solution will probably never be possible.

REFERENCES

Anderson, D., Billingham, R. E., Lampkin, G. H., and Medawar, P. B. (1951). *Heredity*, **5**, 379.
Armitage, P., and Doll, R. (1954). *Brit. J. Cancer*, **8**, 1.
Berenblum, I., and Shubik, P. (1949). Ibid., **3**, 109.
Beveridge, W. I. B., and Burnet, F. M. (1946). *Spec. Rep. Ser. Med. Res. Coun. (Lond.)*, No 256.
Bielschowsky, F., Griesbach, W. E., Hall, W. H., Kennedy, T. H., and Purves, H. D. (1949). *Brit. J. Cancer*, **3**, 541.
Billingham, R. E., Brent, L., and Medawar, P. B. (1956). *Phil. Trans. B*, **239**, 357.
Bird, M. J., and Fahmy, O. G. (1952). *Proc. roy. Soc. B*, **140**, 556.
Biskind, M. S., and Biskind, G. S. (1944). *Proc. Soc. exp. Biol. (N.Y.)*, **55**, 176.
Black, M. M., Opler, S. R., and Speer, F. D. (1954). *Surg. Gynec. Obstet.*, **98** 725.
Burnet, F. M. (1956). *Enzyme Antigen and Virus*. Cambridge Univ. Press.
—— and Fenner, F. J. (1949). *Production of Antibodies*. Macmillan. Melbourne.
Clark, D. E. (1955). *J. Amer. med. Ass.*, **159**, 1007.
Coons, A. H. (1954). *Ann. Rev. Microbiol.*, **8**, 333.
Cowdry, E. V. (1955) *Cancer Cells*. Saunders, Philadelphia.
Duran-Reynals, F. (1953). In *Physiopathology of Cancer*, edited by Homburger and Fishmann, p. 298. London.
Ebert, J. D. (1954). *Proc. Nat. Acad. Sci.*, **40**, 337.
Faber, M. (1956). Cited in *British Medical Journal*, **2**, 704.
Fisher, J. C., and Hollomon, J H. (1951). *Cancer*, **4**, 916.
Furth, J. (1954). *J. nat Cancer Inst.*, **15**, 687.
Ginder, D. R., and Friedewald, W. F. (1951). *Proc. Soc. exp. Biol. (N.Y.)*, **77**, 272.
Gorbman, A. (1949). Ibid., **71**, 237.
Green, H. N. (1954). *British Medical Journal*, **2**, 1374.
Greenstein, J. P. (1954). *Biochemistry of Cancer*. Academic Press, N.Y.
Gross, L. (1954). *Proc. Soc. Exp. Biol. (N.Y.)*, **86**, 734.
Habich, H. (1953). *Schweiz. med. Wschr.*, **83**, 1253.
Hauschka, T. S. (1953). *J. nat. Cancer Inst.*, **14**, 723.
Homburger, F., and Fishman, W. H. (editors) (1953). *The Physiopathology of Cancer*. London.
Jones, H. B. (1956). *Trans. N.Y. Acad. Sci.*, **18**, 298.
Kanzow, U. (1954). *Klin. Wschr.*, **32**, 154.
Kaplan, A. S. (1955). *Virology*, **1**, 377.
Koprowski, H. (1955). *Nature (Lond.)*, **175**, 1087.
Krebs, C. (1943). *Acta radiol. (Stockh.)*, **24**, 190.
Law, L. W. (1952). *Nature. (Lond.)*, **169**, 628.
Leighton, J. (1951). *J. nat. Cancer Inst.*, **12**, 545.
—— (1954). Ibid., **15**, 275
Lindeman, V. F. (1929). *Physiol. Zool.*, **2**, 255.
Mackay, I. R. (1956). *Aust. Ann. Med.*, **5**, 244.
March, H C. (1950). *Amer. J. med. Sci.*, **220**, 282.
Medical Research Council (1956). *The Hazards to Man of Nuclear and Allied Radiations*. H.M.S.O., London.
Metcalf, D. (1955). *Med. J. Aust.*, **1**, 874.
Moloney, W. C. (1955). *New Engl. J. Med.*, **253**, 88.
Moscona, A. (1953). *Exp. Cell. Res.*, **3**, 535.
—— (1956). *Proc. Soc. exp. Biol. (N.Y.)*, **92**, 410.
Pollock, M. R. (1953). *Stages in Enzyme Adaptation*, p. 150. Symp. Soc. Gen. Microbiol. Adaptation in Microorganisms, Cambridge.
Rawles, M. E. (1944). *Physiol. Zool.*, **17**, 167.
Rous, P., and Kidd, J. G. (1938). *J. exp. Med.*, **67**, 399.
Sanford, K. K., Likely, G D., and Earle, W. R. (1954). *J. nat. Cancer Inst.*, **15**, 215.
Shope, R. E. (1933). *J. exp Med.*, **58**, 607.
Stewart, A., Webb, J. Giles, D., and Hewitt, D. (1956). *Lancet*, **2**, 447.
Stewart, S E. (1954) *J. nat. Cancer Inst.*, **14**, 1187.
Stocks, P., and Campbell, J. M. (1955). *British Medical Journal*, **2**, 923.
Syverton, J. T., Wells, E. B., Koomen, J., Dascomb, H. E., and Berry, G. P. (1950). *Cancer Res.*, **10**, 474.
Weiler, E. (1956). *Z. Naturforsch.*, **11B**, 31.
Weiss, P. A. (1947). *Yale J. Biol. Med.*, **19**, 235.
—— and Andres, G. (1952). *J. exp. Zool.*, **121**, 449.
Willier, B. H., Weiss, P. A., and Hamburger, V. (1955). *Analysis of Development*, p. 1955. Saunders, Philadelphia.
Woodruff, M. F. A., and Woodruff, H. G. (1950). *Phil. Trans. B*, **234**, 559.

At the meeting of the council of the Royal College of Nurses last month final approval was given to a new training scheme which would lead to State registration and the health visitor's certificate. It is being organized by the College with the help of King's College Hospital. A four-year course is envisaged (excluding six months' training for part I midwifery). An introductory term at the Royal College of Nursing would be followed by three years' training at King's College Hospital. Then would come seven months of more specialized training at the College as a health visitor, leading to the health visitor's examination. To ensure continuity and integration of study, one health-visitor tutor at the College would be responsible for the students throughout; during the hospital period she would remain in contact with them in co-operation with the hospital sister-tutors. She would undertake certain lectures at the preliminary training school of the hospital, and also join in the case-study discussions. The scheme is now to be submitted to the Royal Society of Health and the Ministry of Health, with a view to beginning the course in September, 1958.

LONG-TERM RESULTS IN EARLY CASES OF RHEUMATOID ARTHRITIS TREATED WITH EITHER CORTISONE OR ASPIRIN

A THIRD REPORT BY THE JOINT COMMITTEE OF THE MEDICAL RESEARCH COUNCIL AND NUFFIELD FOUNDATION ON CLINICAL TRIALS OF CORTISONE, A.C.T.H., AND OTHER THERAPEUTIC MEASURES IN CHRONIC RHEUMATIC DISEASES*

A comparative study of the value of cortisone and aspirin therapy in early cases of rheumatoid arthritis was started in 1951 by the Joint Committee of the Medical Research Council and Nuffield Foundation on Clinical Trials of Cortisone, A.C.T.H., and Other Therapeutic Measures in Chronic Rheumatic Diseases. The findings during the first and second years of therapy have already been published (Joint Committee, 1954, 1955). Although the therapeutic trial in its original form was not continued after the second year, most of the 61 patients originally taken into the trial have been followed by the physicians at the five participating centres, and a review of the condition of these patients at between three and four years from the start of therapy has provided some interesting information. The patients originally admitted to the trial form a well-defined and homogeneous group of early cases, since only patients with a disease duration of not less than three and not more than nine months were included. In addition the patients had to have a polyarthritis of rheumatoid type affecting at least four joints, with bilateral involvement of hands, feet, ankles, or wrists, and they had to be between 17 and 59 years of age at the time of entry into the trial. The sheep-cell agglutination test was carried out during the first year in 53 of the 61 patients studied and a positive result was recorded at least once in three-quarters of them.

Completeness of Follow-up

The number of patients available for assessment during the three to four years of study is shown in Table I. As previously reported, 3 of the 31 patients allocated to aspirin were lost during the first year of therapy. One woman aged 60 who did well emigrated to New Zealand. A woman aged 53 had a psychological breakdown after three months of therapy and declined to return. And a man aged 48 whose condition was deteriorating felt he was deriving no benefit from the tablets after six months. During the second year there were no losses, but during the third year five patients were lost sight of. In two women aged 45 the disease had been in complete remission throughout most of the second year, and they were untraceable at the

*The members of the Joint Committee are: Lord Cohen of Birkenhead (chairman), Dr. E. G. L. Bywaters, Dr. W. S. C. Copeman, Sir Charles Dodds, Dr. J. J. R. Duthie, Professor A. Bradford Hill, Mr. H. Osmond-Clarke, Professor F. T. G. Prunty, Dr. J. Reid, Dr. H. F. West; Professor J. H. Kellgren and Mr. W. A. Sanderson (joint secretaries).

The Subcommittee and participating centres were: Professor J. H. Kellgren (chairman), Rheumatism Research Centre, Manchester; Dr. E. G. L. Bywaters, Postgraduate Medical School of London and Canadian Red Cross Memorial Hospital, Taplow; Dr. W. S. C. Copeman, West London Hospital; Dr. J. J. R. Duthie, Northern General Hospital, Edinburgh; Dr. H. F. West, Sheffield Centre for the Investigation and Treatment of Rheumatic Diseases; Professor A. Bradford Hill; and Professor F. T. G. Prunty.

The results of the trial were analysed by Dr. J. T. Boyd, of the Statistical Research Unit of the Medical Research Council, London School of Hygiene and Tropical Medicine, and the Subcommittee is greatly indebted to him for his work.